

## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

Date of mailing (day/month/year) 29 May 2000 (29.05.00)	To:  Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE  in its capacity as elected Office
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International application No. PCT/US99/23252	Applicant's or agent's file reference DEX-0046
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International filing date (day/month/year) 05 October 1999 (05.10.99)	Priority date (day/month/year) 05 October 1998 (05.10.98)
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## Applicant

MACINA, Roberto, A.

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

01 May 2000 (01.05.00)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Pascal Piriou  Telephone No.: (41-22) 338.83.38
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/23252

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

US PATENTS (EAST/BRS), MEDLINE, EMBASE, BIOSIS, CAPLUS

search terms: esbp, espbii, hesf, lipophilin, estramustine binding protein, prostatein, diagnos?, prognos?

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 98/56248 A1 (SMITHKLINE BEECHMAN CORPORATION) 17 December 1998, pages 9 and 16.	1, 5, 6 and 9 ---
---		10
Y,P		
X	WO 98/21331 A1 (INCYTE PHARMACEUTICALS INC.) 22 May 1998, pages 21, 24, 26-28, 31 and 41.	1, 5, 6 and 9 ---
---		10
Y		

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"a"	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

12 JANUARY 2000

Date of mailing of the international search report

11 FEB 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and TrademarksBox PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ANNE L. HOLLERAN

Telephone No. (703) 308-0196

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/23252

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database EMBASE on STN, Elsevier Sci. B.V., SHIINA et al. 'Immunohistochemical analysis of estramustine binding protein with particular reference to proliferative activity in human prostatic carcinoma,' abstract, Prostate, 1997, Vol. 32, No. 1, pages 49-58.	1, 3, 5 and 6
A	PARKER et al. Prostatic steroid binding protein: gene duplication and steroid binding. Nature. 01 July 1982, Vol. 298, pages 92-94, see entire document.	1-6
A,P	ZHAO et al. Lipophilins: Human peptides homologous to rat prostatein. Biochem. Biophys. Res. Commun. 1999, Vol. 256, pages 147-155, especially page 147.	1-6

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US99/23252

**A. CLASSIFICATION OF SUBJECT MATTER:**

IPC (6):

**A61K 51/00, 49/00, 39/395; C12Q 1/ 00, 1/68; G01N 33/53, 33/567, 33/574**

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL :

**424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960**

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**PATENT COOPERATION TREATY**

DEPARTMENT OF COMMERCE  
MAR 23 2001  
U.S. PATENT AND TRADEMARK OFFICE

From the  
**INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**

To: JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053  
Docket System   
Status Report   
Docket Book   
  
NP = 4-501

**PCT**

**NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

(PCT Rule 71.1)

Date of Mailing  
(day/month/year)

**06 MAR 2001**

Applicant's or agent's file reference

**IMPORTANT NOTIFICATION**

DEX-0046

International application No.	International filing date (day/month/year)	Priority Date (day/month/year)
PCT/US99/23252	05 OCTOBER 1999	05 OCTOBER 1998

Applicant

DIADEXUS LLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230
--

Authorized officer ANNE L. HOLLERAN <i>Della Hobbs, Jr.</i>  Telephone No. (703) 308-0196
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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DEX-0046	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/23252	International filing date (day/month/year) 05 OCTOBER 1999	Priority date (day/month/year) 05 OCTOBER 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant DIADEXUS LLC		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

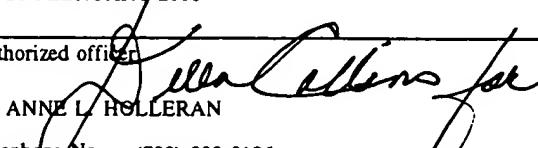
2. This REPORT consists of a total of 4 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

I <input checked="" type="checkbox"/>	Basis of the report
II <input type="checkbox"/>	Priority
III <input type="checkbox"/>	Non-establishment of report with regard to novelty, inventive step or industrial applicability
IV <input type="checkbox"/>	Lack of unity of invention
V <input checked="" type="checkbox"/>	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI <input type="checkbox"/>	Certain documents cited
VII <input type="checkbox"/>	Certain defects in the international application
VIII <input type="checkbox"/>	Certain observations on the international application

Date of submission of the demand 01 MAY 2000	Date of completion of this report 20 FEBRUARY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  ANNE L. HOLLERAN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23252

**I. Basis of the report**

## 1. With regard to the elements of the international application:\*

 the international application as originally filed the description:

pages 1-25, as originally filed  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_

 the claims:

pages 26-28, as originally filed  
 pages NONE, as amended (together with any statement) under Article 19  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_

 the drawings:

pages NONE, as originally filed  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_

 the sequence listing part of the description:

pages 1-2, as originally filed  
 pages NONE, filed with the demand  
 pages NONE, filed with the letter of \_\_\_\_\_

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.  
These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in printed form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4.  The amendments have resulted in the cancellation of:

- the description, pages NONE
- the claims, Nos. NONE
- the drawings, sheets/fig NONE

5.  This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23252

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>2-4, 7, 8 and 10</u>	YES
	Claims <u>1, 5, 6 and 9</u>	NO
Inventive Step (IS)	Claims <u>2-4, 7 and 8</u>	YES
	Claims <u>1, 5, 6, 9 and 10</u>	NO
Industrial Applicability (IA)	Claims <u>1-10</u>	YES
	Claims <u>NONE</u>	NO

**2. citations and explanations (Rule 70.7)**

Claims 1, 5, 6 and 9 lack novelty under PCT Article 33(2) as being anticipated by WO 98/21331 (Incyte Pharmaceuticals, Inc.).

Claim 1 is drawn to a method for diagnosing the presence of prostate cancer or a gynecological cancer. Claim 5 is drawn to a method of monitoring the change in state of prostate cancer or a gynecological cancer. The methods of claims 1 and 5 comprise measuring levels of ESBPII. Claim 6 is drawn to any of the methods of claims 1, 2, 3, 4 or 5 wherein the ESBPII comprises SEQ ID NO: 1 or SEQ ID NO: 2. Claims 9 and 10 are drawn to methods of treating prostate or gynecological cancers comprising administering an antibody which binds to ESBPII. The antibody may be conjugated to a cytotoxic agent.

WO 98/21331 discloses an ESBPII protein which is the same as that of SEQ ID NO: 2 (hSBP). WO 98/21331 teaches methods of diagnosing breast cancer by measuring levels of hSBP (page 21, lines 11-32) and of monitoring patients (page 24, lines 5-28). WO 98/21331 also teaches pharmaceutical compositions comprising antibodies specific for SEQ ID NO: 2 (hSBP) for treatment of breast cancer.

Claim 10 lacks an inventive step under PCT Article 33(3) as being obvious over WO 98/21331. Claim 10 modifies claim 9 because the antibody is conjugated to a cytotoxic agent. However, modification of therapeutic antibodies by adding radiolabels and cytotoxic agents such as a bacterial toxin is well known and does not constitute an inventive step because the use of an antibody specific for SEQ ID NO: 2 is taught by WO 98/21331.

Claims 2-4, 7 and 8 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the methods of diagnosing metastasis, methods of staging, methods of monitoring for the onset of metastasis and methods of imaging prostate cancer.

Claims 1-10 meet the criteria set out in PCT Article 33(4).

(Continued on Supplemental Sheet.)

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23252

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 51/00, 49/00, 39/395; C12Q 1/100, 1/68; GOIN 33/53, 33/567, 33/574 and US Cl.: 424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**----- NEW CITATIONS -----  
NONE

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## PATENT COOPERATION TREATY

OCT 2000

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053

Docket System   
Status Report   
Docket Book

10/28/00 AWS

PCT

## WRITTEN OPINION

(PCT Rule 66)

28 SEP 2000

Applicant's or agent's file reference  DEX-0046		REPLY DUE  within ONE months from the above date of mailing
International application No.  PCT/US99/23252	International filing date (day/month/year)  05 OCTOBER 1999	Priority date (day/month/year)  05 OCTOBER 1998
International Patent Classification (IPC) or both national classification and IPC Please See Supplemental Sheet.		
Applicant DIADEXUS LLC		

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:

- I  Basis of the opinion
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

- When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).
  - How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
  - Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.
  - If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 05 FEBRUARY 2001

Name and mailing address of the IPEA/US  Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized Officer  ANNE L. HOLLERAN  Telephone No. (703) 308-0196
Facsimile No. (703) 305-3230	

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## WRITTEN OPINION

International application No.

PCT/US99/23252

## I. Basis of the opinion

## 1. With regard to the elements of the international application:\*

 the international application as originally filed the description:

pages 1-25

pages NONE

pages NONE

, filed with the demand

 the claims:

pages 26-28

pages NONE

pages NONE

pages NONE

, filed with the demand

 the drawings:

pages NONE

pages NONE

pages NONE

, filed with the letter of

 the sequence listing part of the description:

pages 1-2

pages NONE

pages NONE

, filed with the letter of

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

 the language of a translation furnished for the purposes of international search (under Rule 23.1(b)). the language of publication of the international application (under Rule 48.3(b)). the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

 contained in the international application in printed form. filed together with the international application in computer readable form. furnished subsequently to this Authority in written form. furnished subsequently to this Authority in computer readable form. The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4.  The amendments have resulted in the cancellation of: the description, pages NONE the claims, Nos. NONE the drawings, sheets/fig. NONE5.  This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

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## WRITTEN OPINION

International application No.

PCT/US99/23252

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>2-4, 7, 8 and 10</u>	YES
	Claims <u>1, 5, 6 and 9</u>	NO
Inventive Step (IS)	Claims <u>2-4, 7 and 8</u>	YES
	Claims <u>1, 5, 6, 9 and 10</u>	NO
Industrial Applicability (IA)	Claims <u>1-10</u>	YES
	Claims <u>NONE</u>	NO

**2. citations and explanations**

Claims 1, 5, 6 and 9 lack novelty under PCT Article 33(2) as being anticipated by WO 98/21331 (Incyte Pharmaceuticals, Inc).

Claim 1 is drawn to a method for diagnosing the presence of prostate cancer or a gynecological cancer. Claim 5 is drawn to a method of monitoring the change in state of prostate cancer or a gynecological cancer. The methods of claims 1 and 5 comprise measuring levels of ESBPII. Claim 6 is drawn to any of the methods of claims 1, 2, 3, 4 or 5 wherein the ESBPII comprises SEQ ID NO: 1 or SEQ ID NO: 2. Claims 9 and 10 are drawn to methods of treating prostate or gynecological cancers comprising administering an antibody which binds to ESBPII. The antibody may be conjugated to a cytotoxic agent.

WO 98/21331 discloses an ESBPII protein which is the same as that of SEQ ID NO: 2 (hSBP). WO 98/21331 teaches methods of diagnosing breast cancer by measuring levels of hSBP (page 21, lines 11-32) and of monitoring patients (page 24, lines 5-28).

WO 98/21331 also teaches pharmaceutical compositions comprising antibodies specific for SEQ ID NO: 2 (hSBP) for treatment of breast cancer.

Claim 10 lacks an inventive step under PCT Article 33(3) as being obvious over WO 98/21331. Claim 10 modifies claim 9 because the antibody is conjugated to a cytotoxic agent. However, modification of therapeutic antibodies by adding radiolabels and cytotoxic agents such as a bacterial toxin is well known and does not constitute an inventive step because the use of an antibody specific for SEQ ID NO: 2 is taught by WO 98/21331.

Claims 2-4, 7 and 8 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the methods of diagnosing metastasis, methods of staging, methods of monitoring for the onset of metastasis and methods of imaging prostate cancer.

Claims 1-10 meet the criteria set out under PCT Article 33(4).

## ----- NEW CITATIONS -----

NONE

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WRITTEN OPINION

International application No.  
PCT/US99/23252

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**TIME LIMIT:**

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 51/00, 49/00, 39/395; C12Q 1/100, 1/68; GO1N 33/53, 33/567, 33/574 and US Cl.: 424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960

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**PCT**

WIPO

PCT

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>DEX-0046</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/US99/23252</b>	<u>International filing date (day/month/year)</u> <b>05 OCTOBER 1999</b>	<u>Priority date (day/month/year)</u> <b>05 OCTOBER 1998</b>
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant <b>DIADEXUS LLC</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

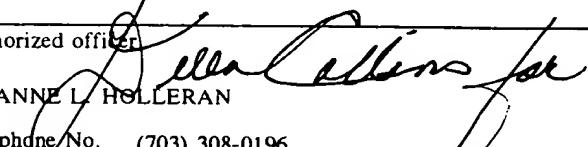
2. This REPORT consists of a total of 4 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand <b>01 MAY 2000</b>	Date of completion of this report <b>20 FEBRUARY 2001</b>
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  <b>ANNE L. HOLLERAN</b>
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23252

## I. Basis of the report

## 1. With regard to the elements of the international application:\*

 the international application as originally filed the description:

pages 1-25

, as originally filed

pages NONE

, filed with the demand

pages NONE

, filed with the letter of

 the claims:

pages 26-28

, as originally filed

pages NONE

, as amended (together with any statement) under Article 19

pages NONE

, filed with the demand

pages NONE

, filed with the letter of

 the drawings:

pages NONE

, as originally filed

pages NONE

, filed with the demand

pages NONE

, filed with the letter of

 the sequence listing part of the description:

pages 1-2

, as originally filed

pages NONE

, filed with the demand

pages NONE

, filed with the letter of

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

 the language of a translation furnished for the purposes of international search (under Rule 23.1(b)). the language of publication of the international application (under Rule 48.3(b)). the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

 contained in the international application in printed form. filed together with the international application in computer readable form. furnished subsequently to this Authority in written form. furnished subsequently to this Authority in computer readable form. The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4.  The amendments have resulted in the cancellation of: the description, pages NONE the claims, Nos. NONE the drawings, sheets Fig NONE5.  This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>2-4, 7, 8 and 10</u>	YES
	Claims <u>1, 5, 6 and 9</u>	NO
Inventive Step (IS)	Claims <u>2-4, 7 and 8</u>	YES
	Claims <u>1, 5, 6, 9 and 10</u>	NO
Industrial Applicability (IA)	Claims <u>1-10</u>	YES
	Claims <u>NONE</u>	NO

**2. citations and explanations (Rule 70.7)**

Claims 1, 5, 6 and 9 lack novelty under PCT Article 33(2) as being anticipated by WO 98/21331 (Incyte Pharmaceuticals, Inc.).

Claim 1 is drawn to a method for diagnosing the presence of prostate cancer or a gynecological cancer. Claim 5 is drawn to a method of monitoring the change in state of prostate cancer or a gynecological cancer. The methods of claims 1 and 5 comprise measuring levels of ESBPII. Claim 6 is drawn to any of the methods of claims 1, 2, 3, 4 or 5 wherein the ESBPII comprises SEQ ID NO: 1 or SEQ ID NO: 2. Claims 9 and 10 are drawn to methods of treating prostate or gynecological cancers comprising administering an antibody which binds to ESBPII. The antibody may be conjugated to a cytotoxic agent.

WO 98/21331 discloses an ESBPII protein which is the same as that of SEQ ID NO: 2 (hSBP). WO 98/21331 teaches methods of diagnosing breast cancer by measuring levels of hSBP (page 21, lines 11-32) and of monitoring patients (page 24, lines 5-28).

WO 98/21331 also teaches pharmaceutical compositions comprising antibodies specific for SEQ ID NO: 2 (hSBP) for treatment of breast cancer.

Claim 10 lacks an inventive step under PCT Article 33(3) as being obvious over WO 98/21331. Claim 10 modifies claim 9 because the antibody is conjugated to a cytotoxic agent. However, modification of therapeutic antibodies by adding radiolabels and cytotoxic agents such as a bacterial toxin is well known and does not constitute an inventive step because the use of an antibody specific for SEQ ID NO: 2 is taught by WO 98/21331.

Claims 2-4, 7 and 8 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the methods of diagnosing metastasis, methods of staging, methods of monitoring for the onset of metastasis and methods of imaging prostate cancer.

Claims 1-10 meet the criteria set out in PCT Article 33(4).

(Continued on Supplemental Sheet.)

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**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 51/00, 49/00, 39/395; C12Q 1/100, 1/68; GO1N 33/53, 33/567, 33/574 and US Cl.: 424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

----- NEW CITATIONS -----

NONE

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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053

Docket System   
Status Report   
Docket Book   
3/11/00 (pub)

RECEIVED  
FEB 14 2000

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing  
(day/month/year)

11 FEB 2000

Applicant's or agent's file reference

DEX-0046

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US99/23252

International filing date  
(day/month/year)

05 OCTOBER 1999

Applicant

DIADEXUS LLC

1.  The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO

34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703) 305-3230

Authorized officer  
ANNE HOLLERAN

Telephone No. (703) 308-0196

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**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DEX-0046	<b>FOR FURTHER ACTION</b>	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/23252	International filing date (day/month/year) 05 OCTOBER 1999	(Earliest) Priority Date (day/month/year) 05 OCTOBER 1998
Applicant DIADEXUS LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1.  Certain claims were found unsearchable (See Box I).
2.  Unity of invention is lacking (See Box II).
3.  The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - filed with the international application.
  - furnished by the applicant separately from the international application,
    - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
    - transcribed by this Authority.

4. With regard to the title,
  - the text is approved as submitted by the applicant.
  - the text has been established by this Authority to read as follows:  
Title does not accurately reflect claimed subject matter.

New Title: A NOVEL METHOD OF DIAGNOSING, MONITORING, STAGING AND TREATING GLYNECOLOGICAL AND PROSTATIC CANCERS

5. With regard to the abstract,

- the text is approved as submitted by the applicant
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. \_\_\_\_\_

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/23252

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet

US CL :Please See Extra Sheet

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

US PATENTS (EAST/BRS), MEDLINE, EMBASE, BIOSIS, CAPLUS

search terms: esbp, espbii, hesf, lipophilin, estramustine binding protein, prostatein, diagnos?, prognos?

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ---	WO 98/56248 A1 (SMITHKLINE BEECHMAN CORPORATION) 17 December 1998, pages 9 and 16.	1, 5, 6 and 9 ---
Y,P ---		10
X ---	WO 98/21331 A1 (INCYTE PHARMACEUTICALS INC.) 22 May 1998, pages 21, 24, 26-28, 31 and 41.	1, 5, 6 and 9 ---
Y		10

 Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

12 JANUARY 2000

Date of mailing of the international search report

11 FEB 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Authorized officer

ANNE L. HOLLERAN

Facsimile No. (703) 305-3230

Telephone No. (703) 308-0196

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/23252

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database EMBASE on STN, Elsevier Sci. B.V., SHIINA et al. 'Immunohistochemical analysis of estramustine binding protein with particular reference to proliferative activity in human prostatic carcinoma,' abstract, Prostate, 1997, Vol. 32, No. 1, pages 49-58.	1, 3, 5 and 6
A	PARKER et al. Prostatic steroid binding protein: gene duplication and steroid binding. Nature. 01 July 1982, Vol. 298, pages 92-94, see entire document.	1-6
A,P	ZHAO et al. Lipophilins: Human peptides homologous to rat prostatein. Biochem. Biophys. Res. Commun. 1999, Vol. 256, pages 147-155, especially page 147.	1-6

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**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US99/23252

**A. CLASSIFICATION OF SUBJECT MATTER:**  
IPC (6):

A61K 51/00, 49/00, 39/395; C12Q 1/100, 1/68; GOIN 33/53, 33/567, 33/574

**A. CLASSIFICATION OF SUBJECT MATTER:**  
US CL :

424/1.49, 9.1, 130.1, 139.1, 152.1, 178.1, 182.1; 435/4, 6, 7.1, 7.2, 7.21, 7.23, 960

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